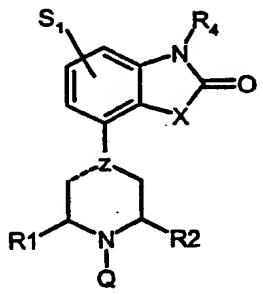
New piperazine and piperidine compounds

The present invention relates to a new group of piperazine and di-dehydropiperidine derivatives having interesting pharmacological properties due to a combination of both partial dopamine D_2-receptor agonism and partial serotonin 5-HT_{1A}-receptor agonism mediated activities. In addition, affinity for adrenergic α_1-receptors is present.

It is known from EP 0189612 that piperazine derivatives substituted at one nitrogen with a phenyl-heterocyclic group, and unsubstituted at the other nitrogen atom, have psychotropic activity.
Further it is known from EP 0190472 that benzofuran- and benzodioxole-piperazine derivatives substituted at the other nitrogen atom of the piperazine group, have also psychotropic activity.
Finally it is known from EP 0169148 that 1,3-dihydro-4-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-2H-indol-2-one and similar compounds have analgetic properties.

It has now surprisingly been found that a small group of piperazine and piperidine derivatives having formula (I)



(I)

wherein
- S_1 is hydrogen, halogen, alkyl (1-3C), CN, CF_3, OCF_3, SCF_3, alkoxy (1-3C), amino or mono- or dialkyl (1-3C) substituted amino, or hydroxy,
- X represents NR_3, S, CH_2 , O, SO or SO_2, wherein R_3 is H or alkyl (1-3C),
- .....Z represents =C or -N,
- R_1 and R_2 independently represent H or alkyl (1-3C), or R_1 and R_2 together can form a bridge of 2 or 3 C-atoms,
- R_4 is hydrogen or alkyl (1-3C),

- Q is methyl, ethyl, ethyl substited with one or more fluorine atoms, cyclopropyl - methyl, optionally substituted with one or more fluorine atoms,
with the proviso that when S_1, R_1, R_2 and R_4 are hydrogen, ...Z is =C and Q is ethyl, X cannot represent CH_2,
and salts and prodrugs thereof have a combination of partial dopamine D_2-receptor agonism and partial serotonin 5-HT_{1A}-receptor agonism activities.

Preferred compounds according to the invention are compounds of the formula (I) wherein S_1, R_1, R_2 and R_4 are hydrogen, X represents oxygen, and .....Z and Q have the above meanings, and the salts thereof.
Especially preferred are the compounds wherein S_1, R_1, R_2 and R_4 are hydrogen, X is oxygen, ...Z represents -N and Q is methyl or ethyl and salts thereof. The most preferred compound being the one wherein Q is methyl.

Compounds according to the invention show affinities for both the dopamine D_2 receptor (pKi range 7.5 – 8.5) and the serotonin 5-HT_{1A} receptor (pKi range 7.0 - 8.0) measured according to well-defined methods (e.g.: Creese I, Schneider R and Snyder SH, [^{3}H]-Spiroperidol labels dopamine receptors in rat pituitary and brain, *Eur J Pharmacol* 1997, **46**: 377-381 and Gozlan H, El Mestikawy S, Pichat L, Glowinsky J and Hamon M, 1983, Identification of presynaptic serotonin autoreceptors using a new ligand ^{3}H-PAT, *Nature* 1983, **305**: 140-142).

The compounds show varying activities as partial agonists at the dopamine D_2 receptor and, surprisingly, at the 5-HT_{1A} receptor. This activity was measured on the formation of adenylate cyclase in cell-lines expressing these cloned receptors (e.g. human D_2 receptors and 5-HT_{1A} receptors expressed in CHO cell line according to the methods described by Solomon Y, Landos C, Rodbell M, 1974, A highly selective adenylyl cyclase assay, *Anal Biochem* 1974, **58:** 541-548 and Weiss S, Sebben M and Bockaert JJ, 1985, Corticotropin-peptide regulation of intracellular cyclic AMP production in cortical neurons in primary culture, *J Neurochem* 1985, **45**:869-874).

The unique combination of both partial dopamine D_2 -receptor agonism and partial serotonin 5-HT_{1A} -receptor agonism results in a surprisingly broad activity in several animal models, predictive for psychiatric and/or neurologic disturbances.
The compounds show a surprisingly high efficacy in a therapeutic model for anxiolytic/antidepressant activity: the conditioned ultrasonic vocalization model in rats (see e.g.: Molewijk HE, Van der Poel AM, Mos J, Van der Heyden JAM and Olivier B

(1995), Conditioned ultrasonic vocalizations in adult male rats as a paradigm for screening anti-panic drugs, *Psychopharmacology* 1995,**117**: 32-40). The activity of the compounds in this model was in the low microgram/kg range, which is surprisingly more active (by a factor 100 to 3000) compared to the compounds previously described in EP 0190472 and EP 0398413.

In addition these compounds also show effects in models predictive for antidepressant activity at higher doses (forced swim test, see e.g.: Porsolt RD, Anton G, Blavet N and Jalfre M, 1978, Behavioural despair in rats: A new model sensitive to antidepressant treatments, *Eur J Pharmacol* 1978, **47**:379-391 and the differential reinforcement of low rates of responding model in rats, see e.g.: McGuire PS and Seiden LS, The effects of tricyclic antidepressants on performance under a differential-reinforcement-of-low-rate schedule in rats, *J Pharmacol Exp Ther* 1980, **214**: 635-641).

At higher doses also dopamine antagonist-like effects were observed (antagonism of apomorphine-induced climbing behaviour in mice, (A), e.g.: Costall B, Naylor RJ and Nohria V, Differential actions of typical and atypical agents on two behavioural effects of apomorphine in the mouse, (B), *Brit J Pharmacol* 1978, **63**: 381-382; suppression of locomotor activity, e.g.: File SE and Hyde JRG, A test of anxiety that distinguishes between the actions of benzodiazepines and those of other minor tranquillisers or stimulants, *Pharmacol Biochem Behav* 1979, **11**: 65-79 and inhibition of conditioned avoidance response in rats, e.g.: Van der Heyden JAM, Bradford LD, A rapidly acquired one-way conditioned avoidance procedure in rats as a primary screening test for antipsychotics: influence of shock intensity on avoidance performance, *Behav Brain Res* 1988, **31**: 61-67). The first two activities, A and B, have previously been reported for partial dopamine D_2 -receptor agonists by Mewshaw et.al, *Bioorg. Med. Chem. Lett.* **8** (1998) 2675.

The compounds are likely to be of value in the treatment of affections or diseases of the central nervous system, caused by disturbances of the dopaminergic and/or serotonergic systems, for example: anxiety disorders (including e.g. generalised anxiety. Panic, Obsessive compulsive disorder), depression, autism, schizophrenia, Parkinson's disease, disturbances of cognition and memory.

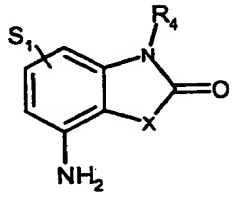
Suitable acids with which the compounds of the invention can form acceptable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric

acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid and naphtalene sulphonic acid.

Prodrugs are derivatives of the compounds having formula (I) wherein R_4 is a group which is easily removed after administration. Suitable prodrugs for example are compounds wherein N-R_4 is one of the following groups: amidine, enamine, a Mannich base, a hydroxy-methylene derivative, an O-(acyloxymethylene carbamate) derivative, carbamate or enaminone.

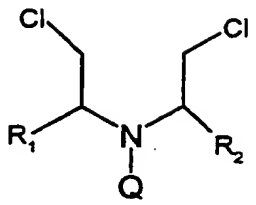
The compounds and the salts thereof can be brought into forms for administration by means of usual processes using auxiliary substances such as liquid and solid carrier materials.

The compounds of the invention can be prepared according to methods known for the synthesis of analogous compounds.
Compounds having formula (I) can be obtained by reacting the corresponding compound wherein Q is hydrogen with a compound Q-Hal, wherein Q is methyl (optionally fluorinated) ethyl, or (optionally fluorinated) cyclopropylmethyl and Hal is halogen, preferably iodine. This reaction can be carried out in a solvent such as acetonitrile in the presence of a base, for example ethyl-diisopropylamine or triethylamine.
The starting compounds wherein Q is hydrogen and ...Z is -N are known or can be obtained as described in EP 0189612. Starting compounds wherein Q is hydrogen and ...Z is $=CH_2$ can be obtained as described below.
The compounds of the invention wherein ...Z is -N, can also be obtained by reacting a compound having formula (II)



(II)

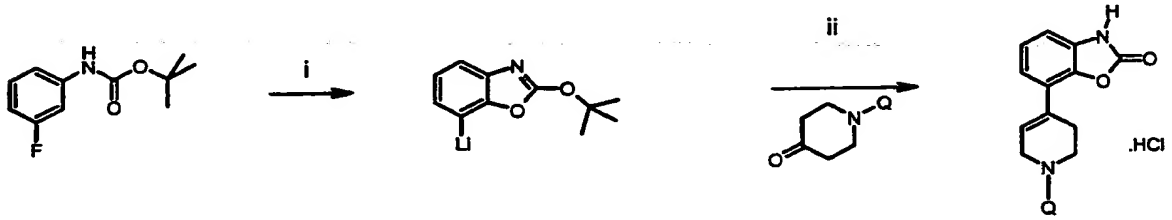
with a compound of the formula (III)



(III)

in which formulae the symbols have the above meanings. This reaction can be carried out in an organic solvent such as chlorobenzene.

The compounds having formula (I) wherein .....Z represents =C can also be obtained according to the method indicated in the following scheme:



The starting compound for step (i) can be obtained according to the procedure described in J. Org. Chem. 45, (1980), 4789, and step (i) itself can be carried out as described in J. Org. Chem., 47, (1982), 2804.

Step (ii) is carried out in a manner known for this type of chemical reactions, and is elucidated in Example 3.

The invention will be illustrated in the following Examples:

Example 1:

1.28 g (5 mmol) of I-H.HCl was suspended in 25 ml of acetonitrile and 0.34 ml (4.4 mmol) of ethyliodide together with 5 ml of di-isopropyl ethyl amine were added. The resulting reaction mixture was stirred and refluxed for 18 hrs under a nitrogen atmosphere. The reaction mixture was allowed to reach room temperature after which a small quantity of SiO_2 was added. The resulting suspension was concentrated *in vacuo*

leaving a powder which was put on top of a chromatography column after which a chromatography run was done (SiO_2 , eluent CH_2Cl_2/MeOH 95/5) yielding 0.55 g of a white solid. The latter was crystallized from EtOAc/EtOH (ca. 1/1) to which 1.1 equivalent of 1 M HCl/EtOH was added. The crystals were collected by filtration, washing with respectively EtOAc and di-ethyl ether yielded after drying 0.5 g (42%) of the desired HCl salt of the compound wherein S_1, R_1, R_2 and R_4 are hydrogen, X is oxygen, ...Z is -N, and Q is ethyl, mp 280-2 °C (dec.).

Example 2:

6.0 g (40 mmol) of the compound having formula (II) (wherein S_1 and R_4 are hydrogen and X is oxygen) was dissolved in 150 ml of chlorobenzene after which 8.47 g (44 mmol) of N-methyl-bis(chloro-ethyl)amine monohydrochloride was added. The resulting reaction mixture was stirred and brought to reflux. The water present in the starting materials was separated by means of a Dean-Stark device. After 44 hrs solid material had formed and the reaction mixture was allowed to reach room temperature. The liquid was separated, the residue was washed with toluene after which it was refluxed in ethanol. After cooling the solid material was filtered and subsequently purified by flash column chromatography (SiO_2, eluent: CH_2Cl_2/MeOH/NH_4OH = 97/2.5/0.5). This procedure yielded 4.5 g of solid material which was dissolved in 96% EtOH (ca. 300 ml) after which, while stirring, 2 equivalents of 1M HCl/MeOH were added. Crystallization started and eventually, after filtration and drying, 4.15 g (38%) of the hydrochloride of the desired compound wherein S_1, R_1, R_2 and R4 are hydrogen, X is oxygen, ...Z is -N, and Q is methyl could be isolated, mp 301.5-302.5 °C.

Example 3:

Under an inert atmosphere, 16.5 g (78.2 mmol) of N-(*tert*.butyloxycarbonyl)-*meta*-fluoroaniline were dissolved in 230 ml of dry tetrahydrofuran (THF) after which the solution was cooled to –75 °C (dry ice , acetone). While stirring a commercially available solution of 1.5 M *tert*.butyl-lithium in heptane (ca. 156 mmol, 2 molequivalents) was added slowly, after which the reaction mixture was stirred for 0.5 hr at –70 °C, and subsequently for an additional 2 hrs at –25 °C. Again the reaction mixture was brought to –75 °C and a solution of 9.6 ml of N-methylpiperidone (78.2 mmol, 1 molequivalent) in ca. 25 ml of dry THF. The reaction mixture was allowed to reach room temperature and stirred for an additional 16 hrs. Subsequently a solution of 1.5 ml (83 mmol) of H_2O in 50 ml of MeOH was added slowly to the reaction mixture, after which 100 ml of SiO_2 was added. The suspension was evaporated to dryness after which the resulting powdery residu was put on top of a chromatography column

after which a "flash"-chromatography run was done (SiO_2 , first eluent: EtOAc, second eluent: MeOH/EtOAc/tri-ethylamine 15/85/1) yielding 12.4 g of a dark yellow oil.
While stirring, 4.7 g (ca. 15.5 mmol) of the obtained product were dissolved in 100 ml of dioxan after which 100 ml of concentrated HCl was added, the resulting mixture was refluxed for 1 hr. The reaction mixture was allowed to reach room temperature after which it was concentrated *in vacuo*, yielding a solid residu. The residu was suspended and stirred in *i*-propanol after which the solid material was filtered and subsequently washed with respectively EtOAc, di-ethyl ether and hexane. After drying 3.1 g of residu was left of which 1.5 g was suspended in EtOH, the latter suspension being refluxed for 1 hr. The mixture was allowed to reach room temperature after which it was filtered, yielding a residu which was washed with absolute EtOH and di(*i*-propyl) ether respectively. After drying 1.1 g (53%) of the desired compound wherein S_1, R_1, R_2 and R_4 are hydrogen, X is oxygen, ...Z is =C, and Q is methyl was obtained, ^{1}H-NMR(400 MHz, D_2O) :
^{1}H-NMR(400 MHz, D_2O): δ 2.96 (broad, 2H, H-5); 3.04 (s, 3H, H-7); 3.3-4.3 (broad, 4H, H-2, H-6); 6.4 (m, 1H, H-3); 7.14 (d, 1H, H-8 or H-10, J=8 Hz); 7.2 (d, 1H, H-10 or H-8, J=8 Hz); 7.26 (t, 1H, H-9, J=8 Hz), using the numbering as indicated in the following formula: